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MANAGEMENT STRATEGIES FOR CANDIDATES FOR PROTEASE INHIBITORS AND REQUIRING TREATMENT FOR *MYCOBACTERIUM TUBERCULOSIS*

Introduction

Although co-infection with HIV and TB has not been a major problem in Canada, there are indications of increasing rates of HIV-related TB. This is especially true for high-risk groups, including intravenous drug users. The availability of protease inhibitors, a potent new antiretroviral therapy, and their documented interaction with rifamycin-type antimycobacterial drugs has given rise to a therapeutic dilemma. This statement has been drafted with a view to providing a balance between the public-health implications of treating active infectious cases of TB with a sub-optimal, non-rifampin regimen versus a delay in the use of protease inhibitors, while using alternative antiretroviral therapy.

Background

The recent availability of a potent new class of drugs, in the form of protease inhibitors, for HIV-infected persons has created a therapeutic dilemma in the treatment of these persons with *Mycobacterium tuberculosis* and *M. avium-intracellulare*. A number of protease inhibitors, including saquinavir (Invirase™), indinavir (Crixivan™), and ritonavir (Norvir™), have recently been licensed for use in persons infected with HIV. Nelfinavir (Viracept™) is also available in Canada as part of an expanded Health Canada access program. These drugs interfere with viral replication and have had a dramatic effect on the management of HIV-infected persons[1,2]. Updated recommendations for their use have been published recently[3]. Unfortunately, there is potential for significant interaction between these drugs and rifampin, one of the primary drugs in the treatment of active (TB)[3]. The metabolism of protease inhibitors is accelerated by rifamycins, leading to sub-therapeutic levels of protease inhibitors. The mechanism of this interaction is through the hepatic P450 cytochrome oxidase pathway. Through a separate mechanism, protease inhibitors slow the metabolism of the rifamycins; this gives rise to increased drug levels of these agents and a greater risk for toxicity.

This problem reinforces the importance of previous recommendations in this area with regard to prophylaxis[4]. It also requires some definitive direction and recommendation in terms of the management of HIV-infected persons with active TB who are either currently taking these agents or who are candidates for initiating therapy with these agents. The following key principles are important.

The optimum approach is to proactively identify co-infection with TB in HIV-infected persons with regular purified protein derivative skin testing[5]. This screening should be particularly focused on groups at high risk of TB, including Aboriginal persons, intravenous drug users, and immigrants from countries with a high prevalence of TB[6]. Treatment with isoniazid in persons co-infected with TB and HIV substantially reduces the risk of active TB; it also reduces the rate of progression to AIDS and death[7]. Age-matched, HIV-infected persons without active TB have a better survival rate than those who develop active TB[8]. The basis for this statement has been further defined recently[9]. The importance of baseline evaluation to ensure that no active TB is present prior to initiating chemoprophylaxis with isoniazid has been emphasized[10]. The priority is to prevent HIV-infected persons with active TB from starting treatment with isoniazid. All HIV-infected persons should have a chest x-ray, and sputum samples assessed by smear and culture. Once active TB has been ruled out and baseline liver function completed, isoniazid chemoprophylaxis can be started.

In newly diagnosed cases of active TB, the primary public-health concern is that HIV-infected persons become non-infectious and complete a satisfactory course of TB therapy. This can usually be achieved within a couple of weeks from the start of therapy, assuming first-line drugs can be used. Confirmation of a patient's non-infectiousness by negative smears is important, especially if the person is returning to a setting with HIV-positive friends or co-workers. A total of 6 months of therapy is usually adequate. During this time, alternative antiretroviral therapy with agents other than protease inhibitors can be

initiated[3,11]. One such combination could include two nucleoside analog reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor.

Recommendations

The following recommendations apply to several different categories of HIV-infected persons diagnosed with active TB and who are being treated with regimens that include protease inhibitors.

1. Patients who are being satisfactorily treated with an antiretroviral therapy regimen that includes a protease inhibitor are those who have been able to maintain high-level suppression of viral replication as demonstrated by a consistently non-quantifiable plasma viral load (i.e. below the lower limit of detection of the assay, currently at 400 copies/mL). In these patients, the option of replacing the protease inhibitor with a non-nucleoside reverse transcriptase inhibitor is a valid alternative.
2. Patients who are being treated with a regimen that includes a protease inhibitor – typically, two nucleosides plus a protease inhibitor – and who have a plasma viral load over 400 copies/mL are generally said to be incompletely suppressed; therefore, a change in antiretroviral therapy maybe beneficial. In those instances, a change to two new nucleosides plus a non-nucleoside reverse transcriptase inhibitor should be considered.
3. Patients who have exhausted all other antiretroviral therapy options and who are being successfully treated with a regimen that includes a protease inhibitor – either two nucleosides plus a potent protease inhibitor or a dual protease inhibitor based regimen – present an extremely difficult challenge. Abrupt interruption of antiretroviral therapy has not been shown to promote the development of resistance. This would imply that the treatment could be re-introduced successfully several months later, when the anti-TB treatment has been completed or perhaps when the initial intensive 2-month induction phase of the TB therapy has been completed. On the other hand, resistance to antiretroviral therapy will be promoted if the adherence to the regimen is incomplete, or if one or two of the agents are temporarily discontinued. In this case, resistance will tend to be promoted to the remaining agents that the person continues to take. Not including rifampin in the initial regimen has been associated with a greater risk for relapse, and the duration of the treatment must be extended to 18 to 24 months[12].

Because indinavir at a dose of 800 mg t.i.d. appears to have a lower risk of interaction with rifabutin at a dose of 150 mg once a day, it has been suggested that a four-drug regimen for 9 months with rifabutin instead of rifampin may be used. A recent study has indicated a regimen including rifabutin to be similar to one including rifampin for the treatment of active TB[12,13]. A further option is a four-drug regimen to start, and once bacteriologic response and sensitivities are available, the patient can be switched to a continuation phase of isoniazid and ethambutol for 16 months. This regimen can be used only when the organism is sensitive to isoniazid and ethambutol, and when therapy is directly observed to ensure satisfactory completion of this extended period of treatment[4].

The challenge of providing protease inhibitors to the homeless has been outlined recently[14]. In such a "difficult-to-follow population", the emphasis should be on completing chemoprophylaxis for TB and initiating prophylaxis for *Pneumocystis carinii* pneumonia. Only then should the possibility of protease inhibitors be explored.

Because of the uncertainty and the lack of randomized controlled trials to support the recommendations outlined above, physicians caring for persons in the above categories should take the following precautions.

- Patients should be carefully monitored for response to therapy and ongoing improvement both clinically and radiologically.
- Patients should be assessed on a regular basis to ensure bacteriologic conversion has occurred and that there are no relapses.
- Surveillance for relapse of TB should extend for at least 2 years after completion of the therapeutic regimens outlined above.
- Directly observed therapy should be the primary method of delivery for the anti-TB therapy.

Due to the complexity of treatment and the potential problems associated with treatment, particularly where the person has been identified with drug-resistant disease, close liaison with an expert familiar with both TB and HIV therapies is recommended[11].

In summary, there should be greater targeted surveillance of persons at high risk of co-infection with HIV and TB. In the presence of co-infection, chemoprophylaxis should be strongly encouraged. These measures will help to address the current management dilemma. They will also allow a caregiver to assess a patient's likely adherence to a prolonged drug regimen. Where active TB has been diagnosed, the immediate priority should be to complete a satisfactory course of therapy to ensure that the patient becomes non-infectious as quickly as possible and continues on as short a regimen as possible. This recommendation is based on the greater public-health implications of inadequately treated TB. In particular, when therapy is not adequately completed, the greater the risk of transmission of infection and the development of multi-drug resistant disease.

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Source: *TB/HIV Advisory Committee (J FitzGerald, MD, [Chair], A Adrien, MD, C Archibald, MD, G Bally, MD, M Naus, MD, J Montaner, MD, H Njoo, MD, T Tannenbaum, MD, B Thomas, RN, R Wuske, E Zack.)*

Notifiable Diseases Summary

We have excluded this table from the electronic issue of Canada Communicable Disease Report for those readers who do not need this information. For those readers interested in this table, call the FAX*link* (1-613-941-3900 from a fax machine) and select the index to get the access number.

Notifiable Diseases Summaries published to date in the electronic format (FAX*link*) can be found in the index under the same name.

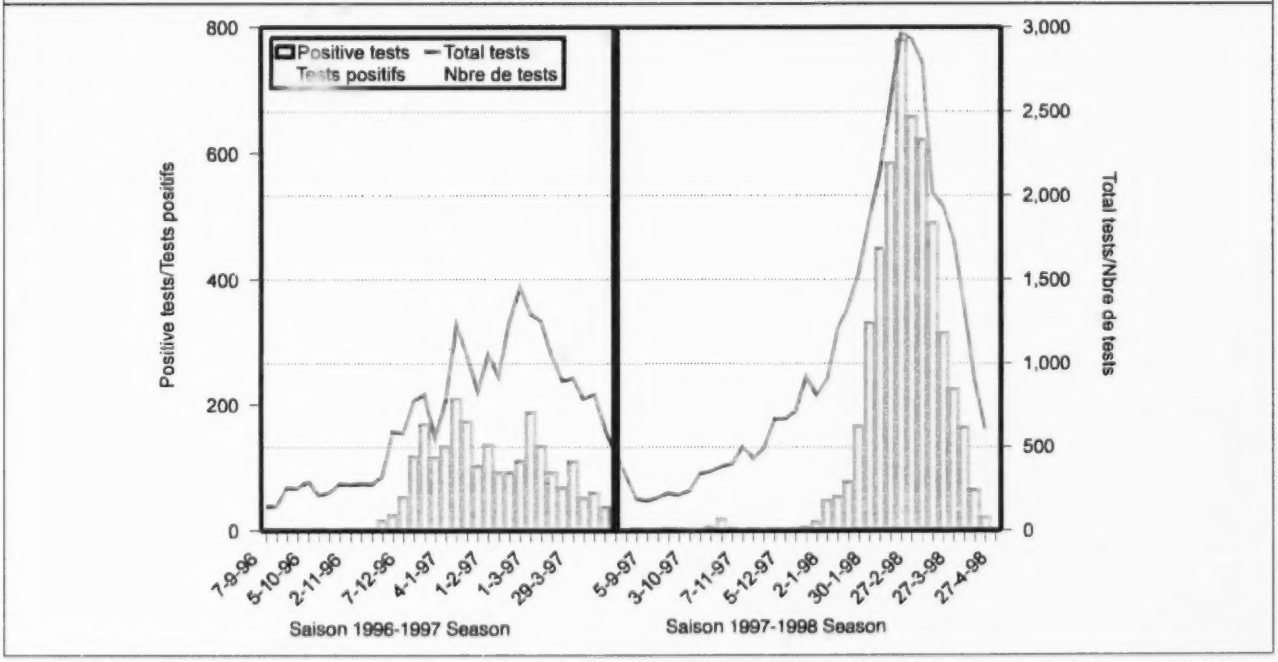
RESPIRATORY VIRUS SURVEILLANCE
FluWatch Project

This update summarizes influenza activity until 17 April 1998. FluWatch has enrolled 191 sentinel physicians representing 140/288 (49%) census divisions in Canada. The physician response rate varies by province and by week. The mean response rate is 64% (41% to 75%).

Figure 1 shows the number of laboratory-confirmed positive tests for influenza and the total number of tests performed during the 1996-1997 and 1997-1998 influenza seasons, as reported to the Division of Disease Surveillance, Laboratory Centre for Disease Control. When the two graphs are compared it is apparent that illness due to influenza virus began later during the 1997-1998 season, and that there were more people tested and more confirmed cases of influenza during this season.

Since September 1997, the FluWatch program has received reports on 36,756 laboratory tests for influenza: 5,087 have been confirmed as influenza A and 17 as influenza B. The provincial distribution of influenza A isolates not subtyped is as follows: Newfoundland (85), Nova Scotia (95), New Brunswick (85), Prince Edward Island (5), Quebec (756), Ontario (2,761), Manitoba (161), Saskatchewan (215), Alberta (556), and British Columbia (236). One hundred and thirty-two influenza A isolates have been further characterized as subtype H3N2. The provincial

Figure 1
Positive and total influenza tests in Canada by week of report, 1996-1997 and 1997-1998



distribution of influenza A H3N2 is as follows: Manitoba (2), Saskatchewan (1), Alberta (2), and British Columbia (127). The provincial distribution of the 17 influenza B isolates is as follows: Quebec (3), Ontario (13), and British Columbia (1).

From November 1997 to 17 April 1998, the National Laboratory for Viral and Zoonotic Pathogens, Laboratory Centre for Disease Control, has completed strain characterization on 371 influenza A isolates: 298 are A/Sydney/5/97 (H3N2)-like, 65 are A/Wuhan/359/95 (H3N2)-like, and 8 are A/Texas/36/91 (H1N1)-like. The provincial distribution of the 298 A/Sydney-like isolates is as follows: British Columbia (9), Alberta (32), Saskatchewan (27), Manitoba (14), Ontario (156), Quebec (36), New Brunswick (4), Prince Edward Island (4), Nova Scotia (6), and Newfoundland (10). The provincial distribution of the 65 A/Wuhan-like isolates is as follows: British Columbia (1), Alberta (6), Saskatchewan (3), Ontario (15), Quebec (32), New Brunswick (1), and Nova Scotia (7). All A/Texas-like isolates are from Ontario.

FluWatch program reports can be accessed through the FluWatch Website:
http://www.hc-sc.gc.ca/hpb/lcdc/bid/dsd/fluwatch/index.html

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